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Patients’ perceptions and patient-reported outcomes in progressive-fibrosing interstitial lung diseases

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Improving patient quality of life and functional status is an important aim of research and development in ILDs with a progressive phenotype. Measures of patients’ perceptions and patient-reported outcomes will be required to understand our interventions. http://ow.ly/neQu30mCS89


ABSTRACT The effects of interstitial lung disease (ILD) create a significant burden on patients, unsettling almost every domain of their lives, disrupting their physical and emotional well-being and impairing their quality of life (QoL). Because many ILDs are incurable, and there are limited reliably-effective, life-prolonging treatment options available, the focus of many therapeutic interventions has been on improving or maintaining how patients with ILD feel and function, and by extension, their QoL. Such patient-centred outcomes are best assessed by patients themselves through tools that capture their perceptions, which inherently incorporate their values and judgements. These patient-reported outcome measures (PROs) can be used to assess an array of constructs affected by a disease or the interventions implemented to treat it. Here, we review the impact of ILD that may present with a progressive-fibrosing phenotype on patients’ lives and examine how PROs have been used to measure that impact and the effectiveness of therapeutic interventions.

Introduction

Some patients with interstitial lung diseases (ILDs) develop progressive fibrosis. A terminology recently used to describe patients with fibrosing ILDs that may present a progressive phenotype is progressive-fibrosing ILD (PF-ILD) [1]. PF-ILD is potentially life-shortening and unquestionably affects how patients feel and function in their daily lives [1]. Activity-limiting dyspnoea, nagging cough and...
debilitating fatigue impair patients’ physical and emotional well-being and quality of life (QoL). Experience with idiopathic pulmonary fibrosis (IPF) shows that, with disease progression, patients lose their independence and are forced to rely on their caregivers to assist them with daily activities and self-care [2].

The broad goals of therapy for any condition are to improve how patients feel or function, or how long they survive. The way to best understand how a condition affects patients (i.e. to learn the symptoms it causes and how it makes them feel physically, what impairments it imposes on their functioning, how it impacts their emotional well-being, its effects on their QoL and which of these effects matter to them) is to ask the experts: the patients themselves [3]. Once patients’ perceptions are known, the path to developing or identifying tools to assess them becomes clearer. Although measuring abstract constructs (like QoL) can be challenging, it can be done. The methods involve capturing patients’ perceptions via surveys or questionnaires [3]. By gathering responses directly from patients, these patient-reported outcome measures (PROs) inherently include patients’ values and judgements [3].

Although lung function measures are useful, they yield incomplete information on how patients with PF-ILD are feeling and functioning [3]. In comparison, PROs produce more comprehensive, personalised information on the outcomes most meaningful to patients [3]. PROs may paint the clearest picture of the influence a disease has on a patient’s life, and they can be used to determine whether (and how) therapeutic interventions induce changes important to patients in the target population.

Here, we review the published data on how PF-ILD affects patients’ lives, how PROs have been used to capture those effects and what additional work is required to improve how we assess outcomes meaningful to patients with PF-ILD. PROs have been used in studies relating to IPF, but there have been few specific studies of PROs in other PF-ILDs [3]. Where appropriate, we have assessed the evidence in IPF as a surrogate for other PF-ILDs.

Impact on patients’ lives

*Patients’ perspectives on diagnosis*

Unfortunately, the emotional toll paid by patients diagnosed with PF-ILD typically begins long before the diagnosis is confirmed. Published data reveal, after coming to medical attention, it takes patients with IPF (on average) longer than a year and multiple visits to physicians to be diagnosed [4].

Having to wait a long time before a diagnosis is made and living that time without a name to explain the cause of their symptoms (leaving patients unaware of what they are up against), generates anxiety for patients who feel they are unable to prepare themselves for what living with the disease entails [5, 6]. Collard et al. [7] administered surveys to 1448 patients with IPF, nearly two-thirds of whom (63.5%) reported being ill-informed about disease management. Patients have also expressed frustrations about a lack of patient-friendly, readily-available, easily-accessible information on IPF at the time of their diagnosis. Similarly, all-comers with connective tissue disease related-ILD, or cohorts of patients with rheumatoid arthritis- or systemic sclerosis-related (SSc)-ILD have expressed confusion around their diagnoses and recognised a need for improved patient–doctor communication [8, 9]. In IPF, the past couple of years have witnessed progress toward answering the call for more educational resources. Such tools are critical to helping patients better prepare themselves for what can be an uncertain future living with the disease. Part of this preparation involves learning healthy coping strategies to deal with negative thoughts and feelings. The involvement of practitioners, including experienced nurses or behavioural health experts, who are trained to help patients navigate the emotional effects of living with a progressive, chronic illness assures adequate support in selected cases.

*Day-to-day life*

Cough and activity-limiting dyspnoea have immense impact on the everyday lives of patients with IPF and other ILDs [2, 10–12]. Cough can affect sleep, willingness to participate in social activities [9] and thus, physical and emotional well-being. Fatigue can be equally debilitating and lead to decreased social participation, physical deconditioning, low mood and isolation [2, 10, 12, 13].

In patients with PF-ILD, dyspnoea limits physical activity in many ways [8, 9]. Some patients avoid certain activities altogether, because the dyspnoea those activities induce is overwhelming; many patients describe having to slow down or stop and rest (perhaps multiple times) to complete an activity. For patients with IPF, this is frustrating and compounds the burden of facing an uncertain future that will probably include worsening health, the need for supplemental oxygen and shortened survival [10].

As the disease progresses, patients’ declining physical functioning limits their ability to look after themselves, forcing them to rely on others (most often a spouse) for help [2]. In the latter stages of IPF, performing basic tasks, such as showering or simple household chores, becomes a struggle [2, 10].
Besides posing a substantial threat to patients’ physical well-being, PF-ILD can negatively impact patients’ mental well-being. Patients may suffer from bouts of anxiety and/or depression and develop feelings of grief and anger [9, 12]. Living with, and coming to terms with a terminal illness, is remarkably difficult [6]. Patients with IPF struggle to cope with the loss of independence and grieve the loss of the lives they once enjoyed [2, 14]. Patients can also feel disconnected with family, as they are unable to participate in family life and care for others [9, 10].

Patients’ expectations of treatment
An ideal treatment would prolong survival, improve QoL and functional status, and reduce the frequency and severity of symptoms [10]. Currently, there are no “cures” for PF-ILD. There are no approved treatment options for PF-ILDs, although corticosteroids and immunosuppressive therapies are sometimes used. While the antifibrotic medications, recently approved to treat IPF (pirfenidone and nintedanib), may slow disease progression, neither was associated with consistent, beneficial effects on symptoms or QoL across phase II and III trials, and neither are approved for the treatment of other PF-ILDs. Specific treatments for fibrosing ILDs that may present a progressive phenotype are covered in more detail by Richeldi et al. [15].

Oxygen therapy is commonly given to alleviate dyspnoea in IPF [14]. This treatment relies on access to oxygen, and requires patients to carry, push or pull tanks and to wear a cannula or have a catheter to breathe in the oxygen. Having to use oxygen can leave patients housebound [10]. The idea of being connected to a machine or tank to receive oxygen is unpleasant, and IPF patients would welcome more convenient oxygen delivery systems that would enable them to be more physically mobile and to travel [10].

The authors recognise that the treatments themselves (taking antifibrotics and/or using supplemental oxygen) can be sources of stress and anxiety for patients. Practitioners aware of this possibility, and able to deal with it if it occurs, are likely to help patients remain adherent to therapeutic interventions.

PROs
A PRO is defined as “any report of the status of a patient’s health condition that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else” [16]. PROs aim to ascertain patient’s perspectives on any number of things, including overall health status, symptoms or QoL [3]. Typically, information is gathered via questionnaires or surveys [3]. PROs can be symptom- or disease-specific or generic [14].

How a disease specifically influences patients in their daily lives cannot be fully captured through other measures of disease severity or activity, like tests of pulmonary physiology and chest imaging [3]. Although weak to moderately strong correlations between PRO scores and those tests support the validity of PROs, each is at least peripherally associated with how patients feel and function, the richness of the patient’s perspective on living with a disease can only be captured by gathering their perceptions.

PROs used in clinical trials
The vast majority of ILD-related clinical trials have focused on IPF and generally used lung function and/or mortality as primary end-points. PROs could easily be used in clinical trials to evaluate symptoms, the effectiveness of a drug and progression of disease [16]. However, few interventional trials have been focused on patient well-being [11, 17] and, when used in these studies, PROs have mainly been regarded as lower-tier end-points [3, 11, 12, 14].

PROs that have been used in studies include dyspnoea indices, cough questionnaires, health status instruments, health-related QoL (HRQoL) measures, depression or anxiety questionnaires and sleep surveys [3]. St. George’s Respiratory Questionnaire (SGRQ) has been used in IPF and other PF-ILD trials to assess respiratory health status [11, 18]. Dyspnoea-specific PROs have also been used to evaluate treatment response [11, 19]. The Medical Outcome Study short-form 36 (SF-36) and the EuroQoL-5D are questionnaires that have been used to assess health status and HRQoL [11, 20, 21]. Anxiety and depression have been quantified using the Hospital Anxiety and Depression Scale and the Generalised Anxiety Disorder Questionnaire – 7 item [22]. An overview of the most widely used PROs in IPF are summarised in tables 1 and 2 [14].

ILD-specific PROs
To date, the PROs most commonly used in IPF trials were originally intended for other uses, including assessing outcomes in patients with other respiratory diseases [37, 38]. PROs developed for chronic obstructive pulmonary disease (COPD), including the SGRQ and COPD assessment tests, have been studied in patients with IPF [12, 14]. Despite some items lacking face validity for IPF, the SGRQ appears to perform reasonably well (particularly its Activities domain) as a measure of health status and symptom
A modified version of the SGRQ has been developed particularly for patients with IPF [12]. The reliability and validity of this PRO is comparable with the original SGRQ as demonstrated by certain psychometric parameters (e.g., internal consistency) and correlation with relevant disease severity measures. However, longitudinal response data are needed to further assess its performance in IPF [14].

A questionnaire specifically developed for ILDs is the King’s Brief ILD (K-BILD) health status questionnaire [14, 25]. The K-BILD requires longitudinal evaluation in PF-ILD [11].
<table>
<thead>
<tr>
<th>PRO</th>
<th>Description</th>
<th>Number of items</th>
<th>Domains assessed</th>
<th>Disadvantages</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td><strong>SOBQ</strong> [27] Self-administered rating of dyspnoea associated with activities of daily living</td>
<td>24</td>
<td>21 items assess severity of shortness of breath during specific activities of daily life; three additional items ask about limitations due to: shortness of breath, fear of harm from overexertion and fear of shortness of breath</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mMRC [28]</td>
<td>Assesses the severity of functional dyspnoea using a graded system (grade 0 (not troubled with breathlessness) to grade 4 (too breathless to leave the house))</td>
<td>1</td>
<td>Quick, easy tool for use in daily practice; relates to disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-TDI [29]</td>
<td>BDI: interviewer-administered rating of severity of dyspnoea at a single state, it provides a multidimensional measurement of dyspnoea based on three components that evoke dyspnoea in activities of daily living, in symptomatic individuals</td>
<td>24</td>
<td>BDI: functional impairment, magnitude of task, magnitude of effort; recall: during the past 2 weeks TDI: measures changes in dyspnoea severity from the baseline established by the BDI</td>
<td>Few specific instructions included in the instrument</td>
<td>Measures both baseline and change over time</td>
</tr>
<tr>
<td>Borg Scale</td>
<td>Measures level of dyspnoea scored on a scale from 0 to 10</td>
<td></td>
<td></td>
<td>Only measures dyspnoea during exertion, does not measure dyspnoea over time</td>
<td>Useful during 6-min walk test in daily practice</td>
</tr>
<tr>
<td>FACIT-D [30, 31]</td>
<td>Evaluates dyspnoea severity</td>
<td>FACIT-D short form: 10 items FACIT-D long form: 33 items</td>
<td>Asking patients to evaluate their shortness of breath across a range of functional activities completed over a week</td>
<td></td>
<td>Disease specific measure</td>
</tr>
<tr>
<td>Cough</td>
<td><strong>LCQ</strong> [32]</td>
<td>19</td>
<td>Three domains: physical, psychological and social</td>
<td>Limited experience in IPF Its specific nature may limit its usefulness when a broader assessment of QoL is desired, patients may need to complete multiple questionnaires if more comprehensive assessment is required</td>
<td>Reliable, responsive to changes, easy to complete</td>
</tr>
<tr>
<td>CQLQ</td>
<td>Validated measure of cough-specific QoL</td>
<td>28</td>
<td>Six domains</td>
<td>Good validity for total score in IPF, but not for all domains</td>
<td>Comprehensive; responsive outcome measure</td>
</tr>
<tr>
<td>PRO</td>
<td>Description</td>
<td>Number of items</td>
<td>Domains assessed</td>
<td>Disadvantages</td>
<td>Advantages</td>
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</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS [33]</td>
<td>General fatigue questionnaire</td>
<td>10</td>
<td>Questions reflect physical and mental fatigue</td>
<td></td>
<td>Quick and easy to complete</td>
</tr>
<tr>
<td>FACIT-FS [34]</td>
<td>Questionnaire to assess fatigue in patients with cancer</td>
<td>13</td>
<td></td>
<td>Not specific for ILD</td>
<td>Reliable and valid scale</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS [35]</td>
<td>Measures anxiety and depression in a general medical population</td>
<td>14</td>
<td>Comprises seven questions for anxiety and seven for depression</td>
<td>Should not be used as a diagnostic test; not originally developed in ILD</td>
<td>Reliable screening tool for anxiety and depression; simple and easy to use</td>
</tr>
<tr>
<td>GAD-7 [36]</td>
<td>Measure of GAD</td>
<td>7</td>
<td></td>
<td>Not specific to ILD</td>
<td>Valid and efficient tool for screening for GAD and assessing its severity in clinical practice and research</td>
</tr>
</tbody>
</table>

IPF: idiopathic pulmonary fibrosis; SOBQ: Shortness of Breath Questionnaire (University of California San Diego); mMRC: modified Medical Research Council; BDI-TDI: Baseline Dyspnoea Index-Transition Dyspnoea Index; FACIT-D: Functional Assessment of Chronic Illness Therapy Dyspnoea; LCQ: Leicester Cough Questionnaire; CQLQ: cough-specific quality-of-life questionnaire; FAS: Fatigue Assessment Scale; FACIT-FS: Functional Assessment of Chronic Illness Therapy Fatigue Scale; HADS: Hospital Anxiety and Depression Scale; GAD-7: Generalised Anxiety Disorder-7; QoL: quality of life; ILD: interstitial lung disease. Modified from [14].
Symptom-specific PROs that have been used to assess outcomes in patients with ILDs are summarised in table 2. These include the University of California San Diego Shortness of Breath Questionnaire, the modified Medical Research Council (mMRC) scale, the Mahler Baseline and Transition Dyspnoea indexes and the Borg scale [11, 14]. Recently, the Functional Assessment of Chronic Illness Therapy-Dyspnoea has been shown to possess validity for assessing dyspnoea in patients with SSc [39]. The mMRC score has been shown to predict survival in patients with IPF [40], but has not been verified for use in patients with SSc-ILD [11].

Although cough is a common symptom of many ILDs, questionnaires have not been developed to assess cough severity or impacts specifically for patients with PF-ILD [14]. In the authors’ opinion, characterisation of this potentially debilitating symptom would be beneficial. The Leicester Cough Questionnaire is currently considered suitable for use in clinical trials (particularly in IPF) [11, 14], but the utility of the Cough QoL Questionnaire in other ILDs that may present a progressive-fibrosing phenotype remains to be elucidated [11].

While fatigue is an important symptom, to date, no specific fatigue questionnaires for IPF exist. As with cough, such a tool may or may not be needed. The Fatigue Assessment Scale, originally developed for sarcoidosis, has been used [14]. The Functional Assessment of Chronic Illness Therapy Fatigue Scale has been validated for use in SSc-ILD [11].

An IPF-specific PRO is currently being developed with the input of a multidisciplinary team of patients and carers [41]. An IPF-specific QoL instrument, A Tool to Assess Quality of Life in IPF, and its modified variant, the living with IPF questionnaire [14] have been developed and are in the late stages of US Food and Drug Administration qualification.

**Barriers to PRO use in clinical studies**

**Relevance of existing PROs for assessing HRQoL**

Using disease-specific and validated PROs in the clinical arena could improve quality of care by alerting practitioners to effects of disease that may otherwise go unrecognised. In the research arena, PROs allow measurement of disease-specific effects not captured by other outcomes. Widely used PROs fail to address certain aspects deemed important by patients [11, 12]. For example, in IPF, patients generally experience a non-productive cough; however, some patients report a productive “hacking cough”, which is not captured in current PROs [10, 13]. Some language in the SGRQ, such as “attack” or “attacks of the chest”, do not resonate with IPF patients, as they feel that this does not correctly describe their disease experience [13]. A "sometimes" response option would be useful to capture IPF patients’ perceptions on some true/false items on the SGRQ more accurately [13]. A category missing from HRQoL questionnaires is one that includes items addressing the impact of supplemental oxygen on QoL [13]. Because many patients with PF-ILDs will need supplemental oxygen, it is imperative that the impact of this treatment on patient’s lives is captured [13].

For any PRO to be useful as a research tool, its basic psychometric properties must be confirmed to fall within the acceptable ranges. For PROs that have been used in IPF research, some of these properties remain to be determined [13]. For a PRO to be used as an end-point in longitudinal research, data to support its longitudinal validity must be generated. For tools currently under development, such data are accruing [13].

**Optimising PROs for research and clinical use**

A reliable measure to assess patient experiences with medical interventions would be helpful. Because each patient is an individual, the effects of a disease or its treatment may vary from person to person, depending on several factors. Investigators in the Netherlands have developed the patient experiences and satisfaction with medications measure [42] to assess tolerance and perceived effectiveness of pirfenidone in IPF.

Together with patients, Russell et al. [41] are developing an IPF-specific, patient-reported experience measure (PREM). The PREM aims to assess patient experiences with healthcare, with the hope that it could be used to improve the quality of care provided to patients. Additional studies of these measures are eagerly awaited.

In clinic, PROs could be a useful metric to assess disease status and patient well-being. However, in a busy clinic, PRO administration may not be practical. Shorter PROs may be required, but they may not yield data with the richness or depth that clinicians desire. Having patients complete PROs delivered electronically the day or week prior to a clinic visit could be considered. The assessment of HRQoL by smartphone applications is currently being investigated. Capturing PRO response data with this modality...
could help facilitate clinical assessment, patient–physician communication and monitoring individual HRQoL over the course of treatment [43, 44].

Conclusion

PROs could help clinicians focus on matters of high concern to patients and help investigators determine whether therapies influence the outcomes of the greatest importance to them. Additional research is needed to determine the performance characteristics of existing PROs in patients with ILDs that may present a progressive-fibrosing phenotype.

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References
